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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,401	02/27/2007	Seth Hallstrom	16785.10	8352

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Workman Nydegger
1000 Eagle Gate Tower
60 East South Temple
Salt Lake City, UT 84111

EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,401	HALLSTROM ET AL.	
	Examiner	Art Unit	
	SAMUEL LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7 and 14* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 1, 2, 7, and 14 are pending.

The amendment filed 1/13/11 which amends claims 1 and 2 has been entered. Claim 3 was cancelled by the amendment filed 3/16/10, and claims 4-6, 8-13 and 15-18 were cancelled by the amendment filed 9/30/10. Claims 1, 2, 7, and 14 are under examination.

The 112/1 rejection (new matter) of claims 1, 2, 7 and 14 is withdrawn in light of the amendment of claim 1.

Maintained-Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1, 2, 7 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 deletes "to a subject" after "administering; this renders the claim indefinite because the claimed method is drawn to the treatment of ischemia and thus there must be a "subject" (or patient) who is suffering said ischemia; otherwise, the treatment is incomplete and ambiguous as to whether or not the said treatment is actually carried out. Claims 2, 7 and 14 which depend from claim 1 and do not cure the defect of claim 1 are also rejected.

Maintained-Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 7 and 14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Schlag et al. (US Pat. No. 6358918 B1) in view of Hallstrom et al. (2002) Circulation, 105, 3032-3038).

In patent claims 16-18 and 21, Schlag et al. teach a method of treating an ischemia (cerebral ischemia) comprising administering to a patient in need thereof a pharmaceutical composition comprising at least one (plurality) [see patent claim 16, line 4] thiol nitrosated (i.e., S-nitroso) thiol-group-containing proteins, wherein "at least one" encompasses more than one S-nitroso-proteins that include S-nitroso-albumin (patent claims 21). This is applied to instant claim 1.

At least 95% of the thiol-group-containing proteins are S-nitrosated (patent claim 19) while N-nitrosation, O-nitrosation and/or C-nitrosation level is less than 10% (patent claim 24). A near complete S-nitrosation of albumin is preferred, e.g., > 95% S-nitroso albumin (see patent claims 16, 17, 19 and 21, and col.3, lines 5-6). These are applied to instant claims 2, 7 and 14.

Provided that Schlag et al. do not expressly disclose or provide working example for combined use of S-nitroso-albumin (S-NO-HSA) and S-nitroso-glutathione (GSH) for treating the ischemia.

Schlag et al., however, teach that the increased S-nitrosation level is companied with the higher the "NO-coupled effect" when administering a nitrosated protein preparation comprising said increased S-nitrosation level (col. 2, lines 23-34). Here, said "NO-coupled effect", in the relative art, refers to high level of nitric oxide (NO) production during ischemia which is followed by increase of releasing O_2^- (an oxygen radial) thereby increase of endothelial ischemic damage (p.3032, right col., lines 10-14, Hallstrom et al.). The reduced glutathione (GSH) has ability of destructing radials, e.g., "O_2^-", and GSH serves as the first line of defense against tissue injury (such as ischemia/reperfusion, see abstract, Hallstrom et al.) due to oxygen toxicity caused by said radical (see p.3037, right col., last paragraph, lines 1-10, Hallstrom et al.)

Schlag et al. teach that a nearly complete S-nitrosation of albumin is preferred, e.g., > 95% S-nitroso albumin (see patent claims 16, 17, 19 and 21, and col.3, lines 5-6). Also, Schlag et al. teach use of thiol-group containing proteins (encompassing GSH) for formulating a pharmaceutical composition for treating the ischemia (col.6, lines 56-63).

These teachings are applied to claim 1.

It would have been obvious to one of ordinary skill in the art at the time the invention

was made to combine S-nitroso albumin (S-NO-HSA) and GSH for treating the ischemia. This is because of the reasons below.

While the S-NO-HSA is a powerful tool in treating and reducing the ischemia/reperfusion thereof (p. 3038, last paragraph, lines 6-7, Hallstrom et al.), the increased protein S-nitrosation level comes with the "NO-coupled effect" which can results in an increased level of O_2^- that is a cause of the ischemia (see above). Hallstrom et al. have taught the important role of GSH in destructing the oxygen radials "O_2^-" which causes tissue ischemic damage, thereby serves as the first line of defense against the ischemic damage (see above). Additionally, the primary reference Schlage et al. have taught administration of plurality (see patent claim 16, line 4) of free-thiol group containing molecule that includes GSH (see above). Mixture of nitrosated proteins and proteins capable of being nitrosated (i.e., proteins having free thiol groups but not having been nitrosated) is particularly preferred (see col.2, lines 58-60). These suggest the combination thereof is preferred.

In view of that the primary reference Schlag et al. is directed to using S-NO-HSA to treat an ischemia state, upon reading the Schlag and Hallstrom references, one of ordinary skill in the art would have readily recognized benefit of combination of use of GSH and S-NO-HSA to treat the ischemia. Said benefit is that both GSH and S-NO-HAS actively scavenge superoxide (O_2^-) which contributes to the ischemic injury or damage. Thus, one of ordinary skill in the art would have tried to formulate GHS with S-NO-HSA into the pharmaceutical composition in order to treat the ischemia injury/damage. When tried, it would have led to reasonable expectation of success in treating the ischemia state. The combination of the references' teachings, therefore, renders the claimed method prima facie obvious in the absence of unexpected result.

The applicants' response to the 103(a) rejection above

At pages 4-7, the response filed 1/13/11 submits that Hallstrom et al. neither teach administering the reduced glutathione (GSH) to a subject nor a combination of nitrosated albumin with GSH, but only show a better ratios of GSH:GSSG in a ischemic subject (p.5, 2nd paragraph).

The response asserts that as GSH already exist in vivo, one of ordinary skill in the art would not find it obvious to administer the reduced glutathione with the nitrosated albumin (p.5, 3rd paragraph).

The response discusses synergistic effects of co-administration (the combination) of S-NO-HSA with GSH (p.5. last paragraph, and p.6, 1st paragraph), and asserts that glutathione is not preferred (p.6, 2nd paragraph). Further, the response submits that claims 2, 7 and 14 include additional elements that further distinguish over the art of record (p.6, last paragraph). Thus, the response requests withdrawal of the rejection.

The applicants' arguments are found unpersuasive because of the reasons set forth in the above rejection and reasons below.

The administration of the nitrosated albumin (S-NO-HSA) to a subject in need thereof for treating or/and reducing the ischemia has been taught by Schlag et al. The motivation of the combining use of S-NO-HAS with GSH is based on the fact that GSH mitigates the undesired "NO-coupled effect" that causes an increased level of O_2^- which in turn results in the ischemic tissue damage (see above). Moreover, Schlage et al. have taught administering plurality of free-thiol group containing molecule including GSH, and have taught the mixture of nitrosated protein with non-nitrosated protein/polypeptide (having free thiol group) is particularly preferred (see the corresponding discussion in above103 rejection).

The "synergistic effect" in fact supports the Office's position because in vitro formulation of GSH with S-NO-HSA in a pharmaceutical composition for in vivo treating the ischemia presents the benefit that GHS serves as the first line of defense against tissue injury via reducing the level of detrimental O_2^- redial. In spite of GSH existing in vivo, the formulation of GSH in vitro with S-NO-HSA would allow for adequately scavenging the detrimental effect of O_2^- redial. Thus, it would have been obvious to combine so.

The applicants' argument as to glutathione not being preferred is unpersuasive because GSH is one of therapeutic polypeptides having free thiol groups which are preferably used for pharmaceutical preparation (see col.2, lines 51-54, Schlag et al.). Upon reading Schlag's reference, one of ordinary skill in the art would have appreciate role of GSH in defending tissue against O_2^- radial thereby more efficiently treating ischemia with reasonable expectation of success since said radial is a cause of the ischemia (see the above Hallstrom's teaching).

The limitations of claims 2, 7 and 14 have been taught by the Schlag et al. patent (see above). All the pending claims are thus obvious over the prior art in record. Thus, the combination of the references' teachings renders the claims prima facie obvious; and therefore, the 103 rejection is proper and maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Liu whose telephone number is (571)272-0949. The examiner can normally be reached on Monday-Friday, 9 am to 5:30 pro. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Samuel Wei Liu/
Patent Examiner, Art Unit 1656
/ANAND U DESAI/
Primary Examiner, Art Unit 1656
March 13, 2011